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# Functional Evaluation of Lipid-Lowering Therapy by Pravastatin in the Regression Growth Evaluation Statin Study (REGRESS)

Wim R.M. Aengevaeren, MD; Gerard J.H. Uijen, PhD; J. Wouter Jukema, MD;  
Albert V.G. Bruschke, MD; Tjeerd van der Werf, MD

**Background** Lipid-lowering therapy during 2 years in the Regression Growth Evaluation Statin Study (REGRESS) was associated with less progression of coronary atherosclerosis in the pravastatin group compared with the placebo group. The effect of lipid-lowering therapy on the functional state of the coronary circulation is less well known. The purpose of this study was to evaluate this effect.

**Methods and Results** In a substudy of REGRESS, 69 patients were randomized to pravastatin or placebo. Thirty-seven of these patients were allocated to the medical management stratum. Quantitative coronary angiography, regional myocardial perfusion, exercise testing, and classification of angina pectoris were assessed at baseline and after 2 years of therapy. Regional myocardial perfusion was assessed by digital subtraction angiography after intracoronary papaverine with videodensitometric calculation of the hyperemic mean transit time (HMTT) of contrast. In the medical management stratum, regional myocardial perfusion was assessed in 31 regions in the pravastatin group and 25 regions in the placebo group. The

change in HMTT in the pravastatin group was  $-0.18$  seconds ( $-5\%$ ) and in the placebo group  $+0.52$  seconds ( $+18\%$ ), a difference of  $0.70$  seconds ( $P=.004$ ). The mean difference in change in classification of angina pectoris (scale, 1 to 4) between pravastatin and placebo was  $0.7$  ( $P=.03$ ) in favor of the pravastatin-treated patients. The change in HMTT was correlated with the change in exercise time ( $r=-.65$ ,  $P=.002$ ).

**Conclusions** In patients with symptomatic coronary artery disease, treatment with the HMG-coenzyme A reductase inhibitor pravastatin during 2 years resulted in a preserved regional myocardial perfusion, whereas patients on placebo deteriorated. The classification of angina pectoris improved only in patients receiving pravastatin. In lipid-lowering therapy, the evaluation of myocardial perfusion by assessment of the HMTT reveals a combined measure of functional and structural changes in the coronary circulation. (*Circulation*. 1997;96:429-435.)

**Key Words** • perfusion • exercise • coronary disease • angiography • lipids

In the multifactorial pathogenesis of coronary atherosclerosis, an elevated cholesterol level is a causal factor.<sup>1</sup> Numerous studies have shown that in patients with coronary artery disease, HMG-coenzyme A reductase inhibitors have a beneficial effect on the incidence of cardiovascular events and development of coronary atherosclerosis.<sup>2-7</sup> In several angiographic trials, the reduction of clinical events was more pronounced than would be expected by the modest influence of lipid lowering on progression of atherosclerosis, which suggests the possibility of a plaque stabilizing effect.<sup>7,8</sup> In normal coronary arteries, the endothelium produces endothelium-derived relaxing factor, which protects the vessel wall by inhibiting platelet adhesion and aggregation, smooth muscle cell proliferation, and smooth muscle cell contraction. Atherosclerosis and hypercholesterolemia have a detrimental effect on endo-

thelial function in both the epicardial coronary arteries and the resistance vessels.<sup>9-11</sup> Exercise induces a metabolic vasodilatation in the resistance vessels and a flow-mediated dilatation of the epicardial vessels, which is endothelium dependent.<sup>12</sup> Endothelial dysfunction leads to paradoxical vasoconstriction with impairment of myocardial perfusion and contributes to the pathogenesis of myocardial ischemia. Cholesterol lowering may restore the endothelial function.<sup>13-15</sup> Translated to the clinical situation, lipid-lowering therapy should have a beneficial effect on maximal myocardial perfusion and the occurrence of myocardial ischemia. The impact of lipid-lowering drugs on functional parameters such as myocardial perfusion, exercise-induced ischemia, and anginal complaints in patients with coronary atherosclerosis is not well known. In this study, we evaluated the functional effect of pravastatin therapy and compared the results with the anatomic evaluation by QCA in symptomatic patients with normal to moderately elevated cholesterol.

## Methods

REGRESS is a double-blind, placebo-controlled, multicenter study designed to assess the effect of 2 years of treatment with the HMG-coenzyme A reductase inhibitor pravastatin on progression and regression of angiographically documented coronary atherosclerosis in male patients with a cholesterol level between 4 and 8 mmol/L (155 and 310 mg/dL). Patients participating in this study were recruited from the waiting list of patients scheduled to undergo coronary angiog-

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From the Department of Cardiology, University Hospital Nijmegen, and Interuniversity Cardiology Institute the Netherlands (J.W.J., A.V.G.B.), Utrecht, the Netherlands.

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Correspondence to W.R.M. Aengevaeren, Department of Cardiology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, Netherlands. E-mail w.aengevaeren@cardio.azn.nl

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## Selected Abbreviations and Acronyms

CABG	= coronary artery bypass graft surgery
HMTT	= hyperemic mean transit time
MOD	= minimal obstruction diameter
MSD	= mean segment diameter
PTCA	= percutaneous transluminal coronary angioplasty
QCA	= quantitative coronary angiography
REGRESS	= Regression Growth Evaluation Statin Study

raphy. Patients who were included at the University Hospital Nijmegen underwent, in addition to the REGRESS protocol, assessment of regional myocardial perfusion for functional evaluation of the effect of pravastatin. The study was approved by the ethics committee of the University Hospital Nijmegen, and written informed consent was obtained from all patients. In short, included were 18- to 70-year-old male patients with proven coronary artery disease (at least one coronary diameter stenosis  $\geq 50\%$ ). The study design, definition of clinical events, and methods assessment of lipid levels and QCA have been reported previously.<sup>7</sup> After cardiac catheterization, patients were stratified in three strata—medical management, PTCA, or CABG—and subsequently randomized to pravastatin 40 mg once daily or placebo. Because bypass grafts and PTCA may have a major impact on flow, distribution of flow, and exercise results, patients who underwent these procedures were excluded from functional evaluation of the effect of pravastatin. QCA was evaluated by assessment of MOD and MSD on the basis of per-patient and per-segment measurements.

### Assessment of Myocardial Perfusion

Myocardial perfusion was assessed by digital subtraction angiography with videodensitometric calculation of the HMTT of contrast passage through the capillary bed. This method has been developed in our laboratory in accordance with the principles of the indicator dilution theory and has been validated in model studies, animal experiments, and humans.<sup>16-18</sup> The short-term reproducibility of the method has been evaluated with a relative difference of  $5 \pm 5\%$  for repeated measurements with a correlation coefficient of .97.<sup>18</sup> To exclude autoregulatory changes in the coronary circulation and to ensure a constant and maximal vascular volume, the assessment of myocardial perfusion was performed during maximal hyperemia induced by papaverine. The derived time parameter, HMTT, is inversely related to myocardial perfusion. We used this method to compare the maximal regional myocardial perfusion in the areas of the left anterior descending artery, right circumflex artery, and right coronary artery at baseline and at follow-up. The methods of image acquisition, analysis of the time-density curves, and correction of the HMTT to a mean aortic blood pressure of 100 mm Hg and the final calculations of the regional HMTTs have been described previously.<sup>19</sup> Calculation of the HMTTs was performed with blinding to treatment allocation. Effect analysis of the lipid-lowering treatment was based primarily on the regional change in myocardial perfusion. The patient-based evaluation was performed by averaging the regional HMTT values to one value per patient as a global estimate of myocardial perfusion.

### Exercise Testing

Exercise testing was performed at baseline and at follow up after 2 years. Antianginal medication was not discontinued. An electronically braked bicycle ergometer (Marquette Case 15, Marquette Electronics Inc) was used, along with continuous ECG monitoring. The exercise was started at a load of 50 W, followed by a 10-W increase every minute until maximal exercise was achieved, chest discomfort occurred, or usual criteria for stopping a test were applied. Blood pressure was recorded every 2 minutes, directly after maximal exercise, and

TABLE 1. Baseline Characteristics

	Pravastatin (n=35)	Placebo (n=34)	P*
Age, y	56.5 $\pm$ 8.0	55.0 $\pm$ 7.8	.43
Length, m	173 $\pm$ 6	176 $\pm$ 7	.03
Weight, kg	80.1 $\pm$ 11.1	82.9 $\pm$ 11.0	.33
Blood pressure, mm Hg			
Systolic	135 $\pm$ 22	137 $\pm$ 16	.65
Diastolic	77 $\pm$ 8	80 $\pm$ 10	.20
Previous myocardial infarction, n	20	21	.70
History of hypertension, n	4	8	.19
Diabetes mellitus, n	0	0	1.0
Angina pectoris classification†	2.5 $\pm$ 0.7	2.4 $\pm$ 1.0	.72
Ejection fraction angiographic	0.66 $\pm$ 0.13	0.66 $\pm$ 0.16	.94
Drug treatment			
$\beta$ -Blockers	26	27	.69
Calcium channel blockers	14	16	.87
Long-acting nitrates	21	13	.12

Values are mean $\pm$ SD when appropriate.

\*One-way ANOVA or the Kruskal-Wallis test as appropriate.

†According to the Canadian Cardiovascular Society at the intake visit.

at rest in the second and fifth minute. Automated calculation was performed of ST-segment depression 80 ms beyond the J-point. Variables used for analysis included maximal workload, time until the onset of 0.1-mV (1-mm) horizontal or downsloping ST-segment depression, maximal ST-segment depression, and maximal rate-pressure product. The patients who underwent nonscheduled interventions in the medical management stratum were excluded from the effect analysis. Patients with an abnormal ECG at the baseline exercise test were also excluded from analysis.

### Classification of Angina Pectoris

After randomization at the first visit and at follow-up after 2 years, angina pectoris was classified in all patients according to the Canadian Cardiovascular Society.<sup>20</sup> The data were analyzed in two ways: first, for the whole group, regardless of nonscheduled interventions; second, in the medical management stratum. However, the moment of classification of the angina pectoris was taken before any nonscheduled intervention.

### Statistical Analysis

Comparison of prespecified continuous variables was performed within the groups by two-sided paired *t* tests; between-group analysis was performed by unpaired *t* tests and one-way ANOVA. For categorical comparisons, a  $\chi^2$  test or the Kruskal-Wallis test was performed when appropriate. Correlations were tested with Pearson's correlation coefficient. Regression analysis was used to compare the change in HMTT with change in exercise parameters and change in QCA data. Calculations were performed on a personal computer with the statistical package SPSS for Windows (releases 6.1 and 7.0). A two-sided value of  $P < .05$  was considered significant. Results were expressed as mean $\pm$ SD unless otherwise indicated.

### Results

Sixty-nine patients were included; subsequently, 35 patients were randomized to the pravastatin group and 34 patients to the placebo group. The groups were well matched for demographic variables (Table 1). The final distribution of the study group in the three treatment strata resulted in 37 patients in the medical management stratum (pravastatin,  $n=19$ ; placebo,  $n=18$ ), 16 patients in the PTCA stratum, and 16 patients in the CABG stratum. Fifty-seven patients completed the study according to the protocol: 32 patients in the medical management stratum, 11 in the PTCA stratum, and 14 in

TABLE 2. Mean Lipoprotein Levels Before and During Treatment in the Placebo and Pravastatin Groups

	Pravastatin (n=35)			Placebo (n=34)			Placebo vs Pravastatin
	Baseline	During Treatment	Difference, %	Baseline	During Treatment	Difference, %	
Total cholesterol, mmol/L	6.15±0.80	5.09±0.74	-17*	6.20±1.01	6.26±0.86	+1	<0.001
LDL cholesterol, mmol/L	4.30±0.74	3.29±0.70	-23*	4.38±0.92	4.43±0.81	+1	<0.001
HDL cholesterol, mmol/L	0.89±0.24	0.95±0.19	+7*	0.94±0.24	0.94±0.19	0	0.09
Triglycerides, mmol/L	2.13±0.86	1.90±0.87	-11*	1.95±0.67	1.96±0.64	+1	0.05

Values are mean±SD when appropriate.

\* $P<.05$ .

the CABG stratum. Dropouts were due to refusal of the second cardiac catheterization in 7 patients, death in 3 patients (two sudden deaths—one in the medical management stratum and one in the PTCA stratum—and one death in the CABG stratum in a patient who died shortly after CABG because of heart failure), and noncardiac causes in 2 patients. In the medical management stratum, 6 nonscheduled interventions were carried out: 1 PTCA in the pravastatin group and 4 PTCAs and 1 CABG in the placebo group. Table 2 gives the mean lipid levels at baseline and during the study. Table 3 shows the QCA data of the medical management stratum. During the study, there was no important change in antianginal medication.

### Myocardial Perfusion

In the medical management stratum group, comparative baseline and follow-up digital subtraction angiographies were available in 25 patients. Table 4 gives the results of the region-based HMTT assessment in the perfusion areas of the left anterior descending coronary artery, right circumflex artery, and right coronary artery. The baseline value of regional HMTT in the pravastatin group was  $3.36\pm1.03$  versus  $2.92\pm0.75$  seconds in the placebo group ( $P=.08$ ). In the per-patient evaluation, the HMTT in the pravastatin group ( $n=15$ ) changed from  $3.33\pm0.81$  to  $3.23\pm0.60$  seconds, a difference of  $-0.10$  seconds ( $-3\%$ ;  $P=.75$ ). In the placebo group ( $n=10$ ), the per-patient HMTT changed from  $2.91\pm0.33$  to  $3.39\pm0.59$  seconds, a difference of  $+0.48$  seconds ( $+16\%$ ;  $P=.01$ ). The difference in change between the pravastatin and placebo groups was  $0.58$  seconds ( $P=.045$ ). The baseline values of the pravastatin and placebo groups on a per-patient base were not significantly different ( $P=.14$ ).

In the PTCA stratum group, 11 patients had follow-up cardiac catheterization. PTCA was performed in 12 vessels in these 11 patients. In 1 vessel, repeated PTCA

was performed. Baseline and follow-up regional HMTT values were available in 9 regions of the PTCA vessels and 15 regions of the nonintervention vessels. Table 5 shows the results of regional HMTT in the PTCA stratum.

### Exercise Testing

In the medical management stratum, 24 of 35 patients had a follow-up exercise test without intercurrent PTCA or CABG. If patients had a nonscheduled PTCA or CABG in the medical management stratum, most often this occurred after a period of progressive or unstable angina pectoris, and in this setting, no exercise tests were performed. Table 6 gives the effect analysis of the exercise testing in the medical management stratum. Baseline exercise tests were positive (1-mm horizontal or downsloping ST-segment depression) in only 11 of 30 tests (37%): 6 in the pravastatin group and 5 in the placebo group. At follow-up, exercise tests were positive in 4 patients in the pravastatin group and 3 patients in the placebo group.

In the PTCA and CABG strata, baseline exercise tests were judged as positive in 18 of 29 tests (62%). At follow-up, 12 of 24 available tests converted to negative. None of the negative tests changed to positive. In these strata, no change in exercise response existed between pravastatin and placebo.

### Classification of Angina Pectoris

In the medical management stratum, the angina pectoris classifications (at a scale of 1 to 4) for the pravastatin and placebo groups at baseline were  $2.1\pm0.5$  and  $1.8\pm0.8$ ; at follow-up, they were  $1.4\pm1.0$  and  $1.7\pm1.0$ , respectively. In 3 patients in the placebo group and 1 patient in the pravastatin group, follow-up was not available. The mean difference in change of angina pectoris classification between pravastatin and placebo was  $0.7$  ( $P=.03$ ; Fig 1).

TABLE 3. Results of QCA in the Medical Management Stratum

	Pravastatin				Placebo				Treatment Effect	P
	n	Baseline	Follow-up	Difference	n	Baseline	Follow-up	Difference		
Pre-patient measurement, mm	17				14					
MSD		2.99±0.44	2.97±0.41	−0.02		2.83±0.40	2.83±0.39	0.00	−0.02	NS
MOD		2.05±0.35	1.97±0.43	−0.08		1.87±0.37	1.77±0.42	−0.10*	0.02	NS
Per-segment measurement, mm	152				118					
MSD		2.99±0.94	2.97±0.89	−0.02		2.85±0.99	2.84±1.02	−0.01	−0.01	NS
MOD		2.08±0.87	2.04±0.88	−0.04		1.90±0.81	1.79±0.85	−0.11*	0.07	NS

Values are mean±SD when appropriate.

\* $P<.05$ .



TABLE 4. Regional HMTT Values in the Medical Management Group

	LAD Region	RCx Region	RCA Region	All Regions
Pravastatin, n	12	9	10	31
Baseline HMTT, s	2.89±0.87	3.11±0.94	4.14±0.88	3.36±1.03
Follow-up HMTT, s	2.97±0.59	2.95±0.42	3.65±1.10	3.18±0.86
P	.76	.57	.12	.27
Placebo	10	9	6	25
Baseline HMTT, s	2.84±0.78	2.46±0.44	3.75±0.29	2.92±0.75
Follow-up HMTT, s	3.05±0.44	3.13±0.77	4.56±1.38	3.44±1.04
P	.37	.03	.16	.006
Difference, P*	.71	.04	.03	.004

Values are mean±SD when appropriate. LAD indicates left anterior descending artery; RCx, right circumflex artery; RCA, right coronary artery.

\*Difference in mean change between pravastatin and placebo groups (t test).

In the combined PTCA and CABG stratum (n=32), the baseline classification of angina pectoris was  $3.1\pm0.6$ , whereas in the medical management stratum (n=37), the baseline classification was  $1.9\pm0.7$  (a difference of 1.2,  $P<.001$ ). At follow-up, the classification of angina pectoris was  $1.6\pm0.8$  for the medical management stratum and  $1.3\pm0.5$  for the combination of PTCA and CABG strata (a difference of 0.3,  $P=.12$ ). In the CABG and PTCA strata, angina pectoris reduced from baseline to follow-up in the pravastatin group with  $1.7\pm0.8$  and in the placebo group with  $1.9\pm0.9$  ( $P=.52$ ).

### Clinical Events

Although this substudy was rather small, a remarkable number of clinical events could be registered. In the placebo group, 13 of 34 patients had a total of 15 clinical events versus 7 clinical events in 5 of 35 patients in the pravastatin group ( $\chi^2$ , 3.96;  $P<.05$ , with Yates' correction). The clinical events were the main reason for loss of follow-up in the medical management stratum.

### Correlations and Regression Analysis in the Medical Management Stratum

The change in MSD was correlated with the change in MOD (n=31,  $r=.62$ ,  $P<.001$ ) but not with the change in exercise parameters (n=24) or HMTT (n=25). The change in MOD was correlated with the change in ST-segment depression (n=24,  $r=-.52$ ,  $P=.009$ ). The change in percentage stenosis was also correlated with the change in ST-segment depression (n=24,  $r=.41$ ,  $P=.046$ ) and with the time to 1-mm ST-segment depression (n=6,  $r=.89$ ,  $P=.017$ ). The change in HMTT was correlated with the change in exercise time (n=20,  $r=-.65$ ,  $P=.002$ ; see Fig 2) and with the maximal load (n=20,  $r=-.47$ ,  $P=.037$ ) but not with the other exercise parameters. In the stepwise multiple regression, the change in HMTT was explained by the combination of changes in total exercise time and MOD (n=19, multiple  $r=.76$ ,  $F=0.0007$ ). The parameters included in this stepwise multiple regression were change in exercise time,

change in MOD, change in MSD, and change in LDL level.

### Discussion

The results of this study show that in patients with coronary artery disease and a cholesterol level between 4 and 8 mmol/L, pravastatin had a favorable effect on regional myocardial perfusion compared with placebo. In the pravastatin group, there was a slight increase in regional myocardial perfusion in the absence of arteriographic evidence of regression. The results of the exercise tests and classification of angina pectoris, however, were concordant with the assessment of regional myocardial perfusion. The discrepancy between the improved myocardial perfusion and the progression of coronary artery disease in the pravastatin group might be explained by an improved endothelium-dependent relaxation.

### Myocardial Perfusion

The baseline HMTT values in the placebo group were shorter than those in the pravastatin group, although the difference was not statistically significant. This phenomenon may be explained by the small sample size and more right coronary artery regions in the pravastatin than in the placebo group (13 versus 7, respectively). In general, HMTT values in the right coronary artery region are about 1 second longer, which is the mean time required for contrast passage from the ostium of the right coronary artery to the crux. Because interventions such as CABG and PTCA may also influence myocardial perfusion in remote noninterventional regions, these strata were excluded from effect analysis of pravastatin on myocardial perfusion.<sup>21,22</sup> The results of the determination of myocardial perfusion were better related with exercise parameters than with anatomic parameters. The assessment of the relation of the change in QCA parameters and the change in HMTT is hampered by a few problems. The QCA analysis of progression and regression was a patient-based comparison, whereas changes

TABLE 5. Regional HMTT in the PTCA Stratum

	Baseline HMTT Before Intervention, s	Follow-up HMTT After 2 y, s	HMTT Difference, s	P
Intervention regions (n=9)	4.19±1.66	3.16±1.01	-1.03±0.93	.01
Nonintervention regions (n=15)	3.07±0.56	2.87±0.88	-0.20±0.92	.41

Nonintervention regions are the regional HMTTs of the PTCA stratum. Data of pravastatin and placebo groups are pooled for both the intervention and nonintervention regions. The difference in change between intervention and nonintervention regions was significant ( $P<.05$ ).

TABLE 6. Results of Exercise Testing in the Medical Management Stratum

	Pravastatin (n=14)			Placebo (n=10)			Difference, P†
	Baseline	After 2 y	P*	Baseline	After 2 y	P*	
Resting heart rate, bpm	73±14	66±12	.05	62±13	69±8	.41	.06
Resting systolic blood pressure, mm Hg	136±27	141±42	.42	143±24	129±14	.23	.32
Maximal heart rate, bpm	128±28	126±29	.73	138±25	132±19	.43	.65
Maximal systolic blood pressure, mm Hg	177±27	189±42	.26	188±31	184±36	.75	.11
Total exercise time, s	649±192	632±116	.65	758±241	653±224	.06	.17
ST time, s	399±224	555±133	.58	567±320	397±410	.31	.21
ST max, mm	1.04±1.01	0.72±1.07	.13	0.65±0.75	0.65±0.69	1.0	.34
Maximal heart rate-systolic blood pressure product, mm Hg/min×10 <sup>-3</sup>	22.9±6.8	24.2±8.4	.41	26.2±7.1	24.5±6.8	.51	.12
Maximal load, W	145±34	148±23	.62	164±41	155±37	.22	.19

ST time indicates time to 1-mm ST-segment depression; ST max, maximum ST-segment depression. Values are mean±SD when appropriate. Bicycle exercise ECG at baseline and after 2 years of therapy.

\*Paired *t* test baseline vs 2 y.

†Unpaired *t* test of the differences between baseline and 2 y in the pravastatin and placebo groups.

in MOD may be restricted to one segment. The regional HMTT data were averaged to a mean value per patient on the basis of a mean of 1.6 perfusion areas per patient. The areas of regional HMTT do not necessarily correspond with the vessel segments that were averaged for the per-patient QCA results. Finally, the expected relation of change in myocardial perfusion and coronary diameter is not linear.

Maximal myocardial perfusion is determined by the resistance in both the conductance vessels and the microcirculation. Because of the method of assessment of the HMTT (sublingual isosorbide dinitrate before the coronary angiography and intracoronary papaverine during the image acquisition), the hyperemia is induced by an endothelium-independent vasodilatation of the resistance vessels and a flow-mediated vasodilatation of the epicardial vessels. The flow-mediated response is endothelium dependent.<sup>23</sup> The difference in myocardial perfusion between the pravastatin and placebo groups might be induced by an impaired flow-mediated vasodilatation in the epicardial vessels in response to the induced hyperemia in the resistance vessels in the placebo group. This hypothesis is adapted from Gould et al,<sup>24</sup> who described this phenomenon in relation to dipyridamole infusion intravenously during PET for flow assessment in lipid-lowering therapy by diet. The administration of isosorbide dinitrate just before the coronary

angiogram might have blunted the endothelium-dependent response. However, the difference in change between the pravastatin and placebo groups of regional myocardial reperfusion are remarkable.

### Exercise Testing

Fixed atherosclerotic obstructions and endothelium-dependent relaxation of the resistance and epicardial vessels are determinants of exercise capacity and exercise-induced ischemia. Although the number of patients studied was relatively small, the group of patients on pravastatin showed a trend toward less ischemia, a lower heart rate at rest, and a better preserved exercise tolerance compared with the placebo group. These effects may be due in part to a preserved or improved endothelial function.

### Classification of Angina Pectoris

As could be expected, baseline angina pectoris was worse in the intervention strata (PTCA and CABG) compared with the medical management stratum. Interventions have a major impact on the classification of angina pectoris. No additional benefit of pravastatin could be established in the intervention strata. After 2 years of therapy, the results of the intervention strata were actually better than the medical management stratum. Nonscheduled interventions may cause a confound-

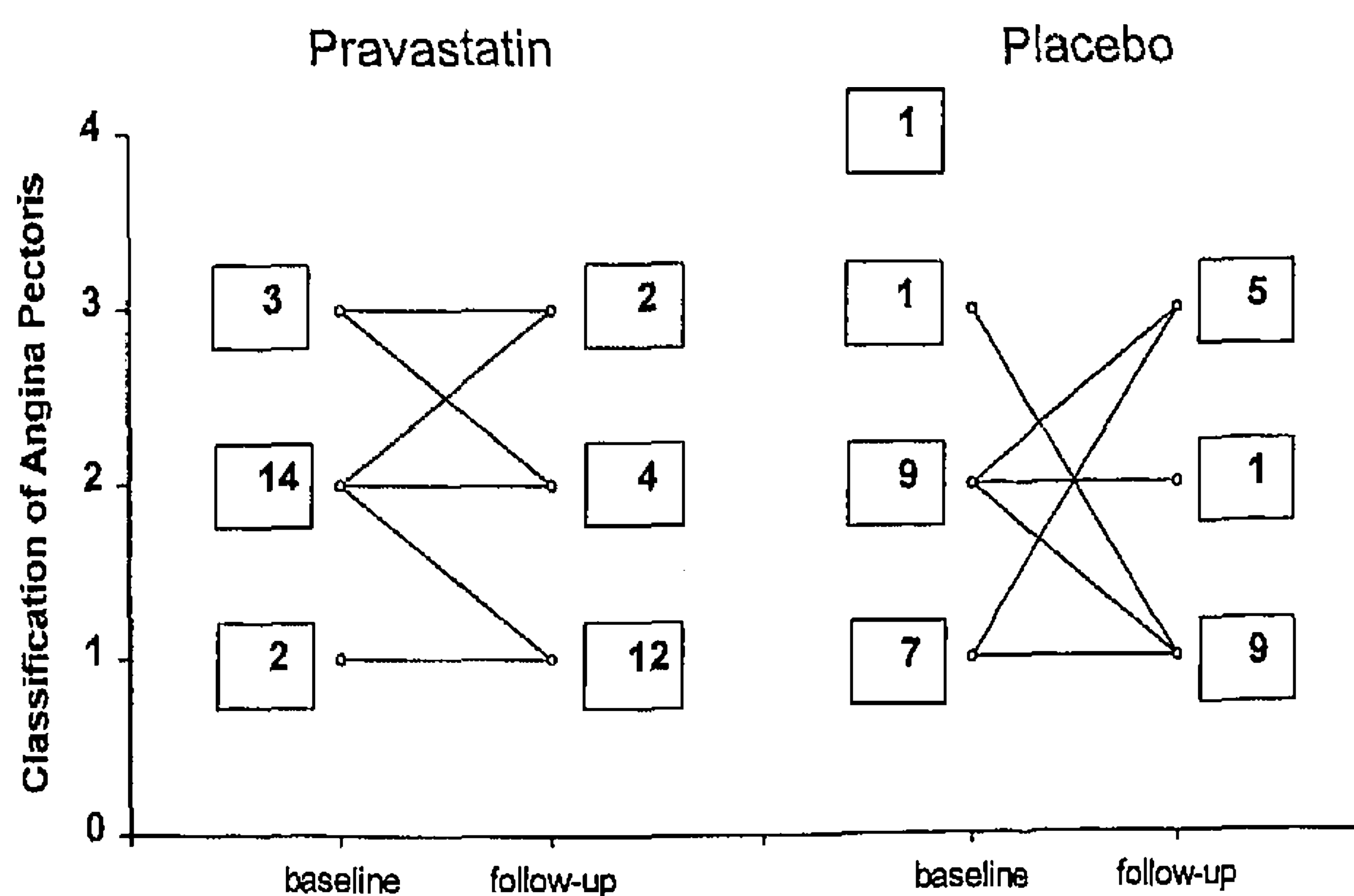


FIG 1. Classification of angina pectoris according to the Canadian Cardiovascular Society. In three patients in the placebo group and one patient in the pravastatin group, follow-up was not available.

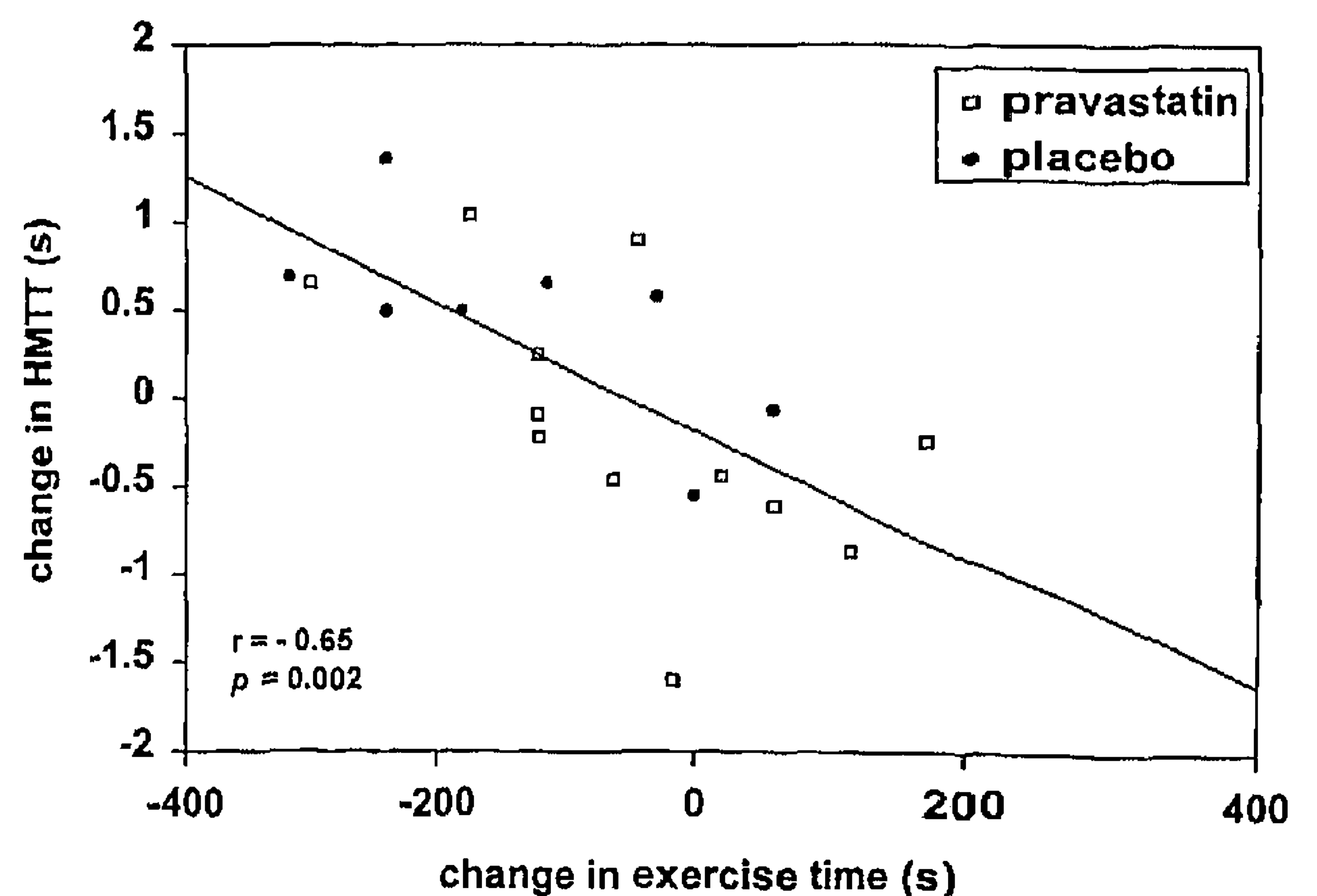


FIG 2. Scatterplot with regression line of the relation between the changes in HMTT and total exercise time. The inverse relation is significant.



ing effect on the analysis of the classification of angina pectoris in the medical management group. For that reason, the classification of angina pectoris before the nonscheduled intervention was considered an end point. The periods of unstable angina were not included because they may represent acute plaque rupture and thrombosis rather than progression of fixed coronary artery atherosclerosis. Nevertheless, the clinical benefit of pravastatin treatment in the medical management stratum is evident.

### Comparison With Other Studies

The number of studies evaluating lipid-lowering therapy with assessment of myocardial perfusion is limited.<sup>24-28</sup> Thallium-201 scintigraphy and PET were used for semiquantitative evaluation. In these studies, myocardial perfusion defects improved in the actively treated patient groups, without significant changes in coronary anatomy, as measured or supposed. In the "long-term intense risk factor modification study," the change in dipyridamole PET images of normalized counts worsened in control subjects by 13.5% and improved in the experimental group by 4.2%, numbers that correspond very well with our results.<sup>27</sup> In some studies, patients in the active treatment group were subjected to a regular exercise program. The effect of training precludes a direct comparison of the effect of lipid-lowering therapy on the exercise parameters.<sup>25,26</sup> In the short-term lipid-lowering study with fluvastatin, the improvement of perfusion defects is established after only 12 weeks of therapy. The improvement was especially noticeable in areas of ischemia.<sup>28</sup> The positive effects of these studies on myocardial perfusion are not elucidated. Suggested mechanisms are improved endothelium-dependent vasodilation, improved collateral circulation, and changes in blood viscosity. The data of the effect of HMG-coenzyme A reductase inhibitors on blood viscosity are conflicting.<sup>29-31</sup> In studies with lovastatin and simvastatin, no effect on blood viscosity was observed, so it is unlikely that a change in blood viscosity caused the changes in myocardial perfusion. Coronary resistance vessels are spared from the development of overt atherosclerosis, but the endothelial function of the microcirculation can be disturbed in the presence of hypercholesterolemia.<sup>9</sup> Thus, improved endothelial function remains the most likely explanation for the improvement in myocardial perfusion, which also may affect collateral circulation.

### Study Limitations

Evaluation of exercise testing in the PTCA and CABG strata was influenced largely by the intervention, so we decided not to include these data in the effect analysis of pravastatin. Follow-up parameters were not available in several patients in the medical management stratum, mostly because of cardiovascular complications. These dropouts occurred predominantly in the placebo group and may have influenced the results of this study. However, these dropouts most likely caused underestimation rather than overestimation of the difference in response between the pravastatin and placebo group.

### Conclusions

In symptomatic men with coronary artery disease and normal to moderately raised cholesterol levels, pravasta-

tin therapy for 2 years resulted in a preserved regional myocardial perfusion, whereas this parameter deteriorated in patients on placebo. The group of patients on pravastatin had fewer clinical events and a trend toward preserved exercise capacity. The change in myocardial perfusion was better related with a change in exercise parameters than with a change in anatomic parameters. In lipid-lowering therapy, assessment of myocardial perfusion is advantageous because it represents a combined measure of the resistance to flow by the epicardial vessels and microcirculation. Functional evaluation of the coronary circulation deserves further investigation as a tool for evaluation of lipid-lowering therapy in patients with coronary artery disease because it might better reflect the clinical benefit for the patient.

### References

1. Badimon JJ, Fuster V, Chesebro, Badimon L. Coronary atherosclerosis: a multifactorial disease. *Circulation*. 1993;87(suppl II):II-3-II-16.
2. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:383-389.
3. Blankenhorn DH, Azen SP, Krams DM, Mack WJ, Cashin-Hemphill L, Hodis H, Deboer LWV, Mahrer PR, Masteller MJ, Vailas LI, Alaupovic P, Hirsch LJ, for the MARS Research Group. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med*. 1993;119:969-976.
4. Waters D, Higginson L, Gladstone P, Kimball B, Le May M, Boccuzzi SJ, Lesperance J, for the CCAIT Study Group. Effects of monotherapy with an HMG CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography: the Canadian Coronary Atherosclerosis Intervention Trial. *Circulation*. 1994;89:959-968.
5. MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet*. 1994;344:633-638. (Erratum. *Lancet*. 1994;344:762).
6. Pitt B, Mancini GB, Ellis SG, Rosman HS, Park JS, McGovern ME. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC I): reduction in atherosclerosis progression and clinical events: PLAC I investigation. *J Am Coll Cardiol*. 1995;26:1133-1139.
7. Jukema JW, Bruschke AVG, van Boven AJ, Reiber JHC, Bal ET, Zwinderman AH, Jansen H, Boerma GJM, van Rappart FM, Lie KI, for the REGRESS Study Group. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels: the Regression Growth Evaluation Statin Study (REGRESS). *Circulation*. 1995;91:2528-2540.
8. Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid lowering and plaque regression: new insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation*. 1993;87:1781-1791.
9. Sellke FW, Armstrong ML, Harrison DG. Endothelium-dependent vascular relaxation is abnormal in the coronary microcirculation of atherosclerotic primates. *Circulation*. 1990;81:1586-1593.
10. Zeiher AM, Drexler H, Sauerbier B, Just H. Effects of age, atherosclerosis, hypercholesterolemia, and hypertension: endothelium-mediated coronary flow modulation in humans. *J Clin Invest*. 1993;92:652-662.
11. Gilligan DM, Guetta V, Panza JA, García CE, Quyyumi AA, Cannon RO. Selective loss of microvascular endothelial function in human hypercholesterolemia. *Circulation*. 1994;90:35-41.
12. Berdeaux A, Ghaleh B, Dubois-Randé JL, Vigué B, Drieu la Rochelle C, Hittinger L, Giudicelli JF. Role of vascular endothelium in exercise-induced dilation of large epicardial coronary arteries in conscious dogs. *Circulation*. 1994;89:2799-2808.
13. Kroon AA, Stalenhoef AFH, Buikema H, Demacker PNM, de Wilde PCM, Leijten PA, van Gilst WH. The effect of cholesterol reduction on endothelial function and progression of atherosclerosis in WHHL rabbits. *Atherosclerosis*. 1993;103:221-230.
14. Egashira K, Hirooka Y, Kai H, Sugimachi M, Suzuki S, Inou T, Takeshita A. Reduction of serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. *Circulation*. 1994;89:2519-2524.



15. Treasure CB, Klein JL, Weintraub WS, Talley JD, Stillabower ME, Kosinski AS, Zhang J, Boccuzzi SJ, Cedarholm JC, Alexander RW. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med*. 1995;332:481-487.
16. Pijls NHJ, Uijen GJH, Hoevelaken A, Arts T, Aengevaeren WRM, Bos HS, Fast JH, van Leeuwen KL, van der Werf T. Mean transit time for assessment of myocardial perfusion by videodensitometry. *Circulation*. 1990;81:1331-1340.
17. Pijls NHJ, Aengevaeren WRM, Uijen GJH, Hoevelaken A, Pijnenburg T, van Leeuwen K, van der Werf T. Concept of maximal flow ratio for immediate evaluation of percutaneous transluminal coronary angioplasty result by videodensitometry. *Circulation*. 1991;83:854-865.
18. Pijls NHJ, Uijen GJH, Pijnenburg T, van Leeuwen K, Aengevaeren WRM, Barth JD, den Arend J, Hoevelaken A, van der Werf T. Reproducibility of the mean transit time for maximal myocardial flow assessment by videodensitometry. *Int J Card Imaging*. 1991;6:101-108.
19. Aengevaeren WRM, Kroon AA, Stalenhoef AFH, Uijen GJH, van der Werf T. Low density lipoprotein-apheresis improves regional myocardial perfusion in patients with hypercholesterolemia and extensive coronary artery disease: the LDL-Apheresis Atherosclerosis Regression Study (LAARS). *J Am Coll Cardiol*. 1996;28:1696-1704.
20. Campeau L. Grading of angina pectoris. *Circulation*. 1976;54:522-523.
21. Uren NG, Marraccini P, Gistri R, de Silva R, Camici PG. Altered coronary vasodilator reserve and metabolism in myocardium subtended by normal arteries in patients with coronary artery disease. *J Am Coll Cardiol*. 1993;22:650-658.
22. Schühlen H, Eigler HL, Whiting JS. Digital angiographic impulse response analysis of regional myocardial perfusion: detection of autoregulatory changes in nonstenotic coronary arteries induced by collateral flow to adjacent stenotic arteries. *Circulation*. 1994;89:1004-1012.
23. Cox DA, Vita JA, Treasure CB, Fish D, Alexander RW, Ganz P, Selwyn AP. Atherosclerosis impairs flow-mediated dilatation of coronary arteries in humans. *Circulation*. 1989;80:458-465.
24. Gould KL, Martucci JP, Goldberg DI, Hess MJ, Edens RP, Latifi R, Dudrick SJ. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease: a potential noninvasive marker of healing coronary endothelium. *Circulation*. 1994;89:1530-1538.
25. Schuler G, Hambrecht R, Schlierf G, Niebauer J, Hauer K, Neumann J, Hoberg E, Drinkmann A, Bacher F, Grunze M, Kübler W. Regular physical exercise and low-fat diet: effects on progression of coronary artery disease. *Circulation*. 1992;86:1-11.
26. Schuler G, Hambrecht R, Schlierf G, Grunze M, Methfessel S, Hauer K, Kübler W. Myocardial perfusion and regression of coronary artery disease in patients on a regimen of intensive physical exercise and low fat diet. *J Am Coll Cardiol*. 1992;19:34-42.
27. Gould KL, Ornish D, Scherwitz L, Brown S, Edens RP, Hess MJ, Mullani N, Bolomey L, Dobbs F, Armstrong WT, Merritt T, Ports T, Sparler S, Billings J. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. *JAMA*. 1995;274:894-901.
28. Eichstädt HW, Eskötter H, Hoffman I, Amthauer HW, Weidinger G. Improvement of myocardial perfusion by short-term fluvastatin therapy in coronary artery disease. *Am J Cardiol*. 1995;76:122A-125A.
29. Fawcett JP, Menkes DB. Does cholesterol depletion have adverse effects on blood rheology? *Angiology*. 1994;45:199-206.
30. Tsuda Y, Satoh K, Takahashi T, Kitadai M, Ichihara S, Ayada Y, Hosomi N, Kawanishi K, Sada, Yamamoto M. Effect of medication with pravastatin sodium on hemorheological parameters in patients with hyperlipoproteinemia. *Int Angiol*. 1993;12:360-364.
31. McDowell IF, Smye M, Trinick T, Shortt JA, Archibald MP, Trimble ER, Nichols DP. Simvastatin in severe hypercholesterolaemia: a placebo controlled trial. *Br J Clin Pharmacol*. 1991;31:340-343.